rarely cures. It gives excellent temporary relief. Unless there are factors—hepatitis, dehydration, lowered kidney function, jaundice, very acute infection, etc.—adding material hazard to cholecystectomy—the gall-bladder had better be removed. If there is evidence of chronic infection—hepatitis, pancreatitis, etc.—the cystic duct should also be drained.

If the correlated conditions add material hazard to cholecystectomy, the gall-bladder should be drained and at the time of election removed. I am not convinced that a positively diseased gall-bladder ever returns to normal. If it does not, its menace as a constant source of focal infection will probably be greater than the immediate hazard of cholecystectomy.

In cases of very acute gall-bladder disease with unsatisfactory general condition, drainage under local anesthesia, with removal at a subsequent time, should give the best mortality records and the most satisfactory ultimate results.

CLOSING NOTE—Now that you have it before you, what is your reaction? From the standpoint of an editor who reads and attempts to evaluate over a million words of copy a year, it is excellent.

Certainly, it is definite enough, brief enough, and "snappy" enough to please a medical Brisbane.

Do you want more of the same type of "Conversaziones," or don't you? Let the editor know your wishes, and while you are about it, in case you approve, suggest other subjects and state whether or not you would be willing to take part.—Editor.

RECENT ADVANCES IN CANCER RESEARCH

By LUDWIG A. EMGE, M. D., *San Francisco*

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Most of the recent findings point toward a cancer-controlling substance of constitutional origin which experimentally can be increased or decreased at will.

Cancer research has opened up new aspects of cancer treatment which may take on concrete forms as research progresses and which ultimately may materialize into more successful methods of treatment.

DISCUSSION *by Edward N. Ewer, Oakland; Alson R. Kilgore, San Francisco; Herbert W. Wall, Los Angeles.*

IN bringing this most important subject before the members of this section it is evident that in the short time allotted it is impossible to present a detailed review of the literature on cancer research. Such a review, at best, would involve the discussion of numerous questions which at this stage of our knowledge must be considered as being of academic interest only. I have, therefore, confined myself to the very recent findings which have a definite practical bearing upon the cancer question and which, I hope, may serve you for a better understanding of the intricate mechanism that underlies cancer production and its treatment. To give a clearer picture of the various phases of cancer research, I have attempted to group the findings in such a way that their relation to each other may be clearly understood.

Heredity, unquestionably, plays one of the most important parts in the production of cancer, although this has not definitely been established for man. Maude Slye's work on mouse cancer proves that cancer tendencies are transmitted just as any other characteristics are passed on from generation to generation. Her work shows that selective breeding can increase or decrease cancer tendencies to a degree where cancer resistance is either completely wiped out or raised to complete protection. The basic factor must be sought in a substance transmitted in the germplasm. This factor is variable in its degree and duration of existence. It seems to be closely akin to the factors which govern the aging of tissues, but does not necessarily depend upon the age of the individual. It is the aging of tissues which brings certain functions of the body to a standstill and with this event the resistance to cancer decreases or disappears. Therefore, any factors which will favor aging of tissues must also favor cancer production. Among these factors, wasting diseases, such as syphilis or severe typhoid for instance, play a definite role. Also frequent and rapid involutions of an organ productive of cicatrix formation, such as occurs in the uterus and the breasts in rapidly recurring pregnancies exerts a definite influence (Stajano). The experimental proof for this assumption may be found in Carrel's recent work on antagonistic growth principles of serum and their relation to old age. In these tissue culture experiments with fibroblasts, two factors stand out clearly, one is that serum loses its proliferative activity on homologous fibroblasts as age advances and the other is that this quality is then replaced by a growth inhibiting action on the same tissue. Since fibroblasts form one of the most important barriers against the advance of despecialized cells which ultimately develop into a malignant structure, we may deduct that any factor which tends to weaken the fibroblastic action must also weaken our cancer defense. With this fundamental finding before us we can no longer consider cancer as a local disease, but must assume that we have to deal with a constitutional disturbance. Bard, who expostulates that the malformation of the cell does not accept the influence of vital induction and, therefore, proliferates without limits, merely expresses the same thought in a reversed order. I shall cite further proof during the progress of this discussion that it is not so much the failure of the despecialized cell to accept the moderating influence of vital fluids as it is the disappearance of some highly specialized hormone in these fluids which allows the aberrant cell to proliferate.

Until very recently the interest of workers in cancer research was mainly concentrated on factors governing the mechanism of local cancer formation. We may accept it as an established fact that acute trauma very rarely leads to malignant growth tendencies, otherwise cancer should be rampant among wounded soldiers. The process which incites cells to undergo abnormal growth tendencies is slow and can best be classed under the general term of chronic irritation. Therefore, the many proofs that have been advanced that this or the other substance is the cause for local cancer "possibly all represent partial and different aspects of the truth" (Hegel). That not every species is susceptible to the same irritants has been exhaustively proven by the many failures in producing skin cancers in animals by the continual application of tar or its derivatives. Some species and sometimes only certain groups within

this species will react to a given irritant while others are completely immune. This was most brilliantly demonstrated by Fibiger in the production of gastric cancer by feeding the nematode spiroptera neoplastica to rats. While one type of rats would, in the majority, develop gastric cancer, other types only responded occasionally, while still others were entirely immune. Clinically, we observe the same phenomenon in the cancer of chimney-sweeps, laborers in the tar and paraffin industry, in the victims of bilharziasis, in the natives of Kashmir suffering from epithelioma of the abdomen and thighs and in x-ray workers with their epitheliomata of the hands. By no means all the individuals exposed to carcinogenic agents develop cancer. Therefore, the carcinogenic agent seems to be only the mediate and not the proximal factor of this disease (Leitch). Leaving out all discussions of what produces actually the reversion of the irritated cell to an undifferentiated cell of the embryonic type as being at present of academic interest only, we may accept that carcinogenic influences are exerted by any long continued irritation to which certain individuals have insufficient constitutional resistance. We also must accept that experimentally at least an irritant may produce either carcinoma or sarcoma, as has been shown in mice. Therefore, the specificity of an irritant in relation to a definite type of malignancy must be questioned.

A further factor in cancer production aside from a weakening of the constitutional resistance is the lowering of local resistance. I have alluded to this above. Wherever organs undergo periodical fluctuations in size, resulting in premature aging of the connective tissue leading to contractions of tissue fibers, or wherever cicatrix results from acute trauma, the circulation is prevented from coming into normal contact with highly specialized tissue. When this tissue is cut off from the vital fluids, its cells lose their differentiated character and revert to a more embryonal type (Lumière). Such cells then acquire the exceptional faculty for growth common to embryonal tissue. They then begin to proliferate and may produce malignant growth, provided the general constitutional factor of protection is lacking. Proof for the protective influence of connective tissue has been offered by Bierich, who noticed the multiplication of connective tissue fibers after continued application of tar before epithelial proliferation took place. On continued irritation the connective tissue reaction came to a standstill and epithelial proliferation occurred and overcame the connective tissue barrier. This investigator succeeded in stimulating connective tissue growth by one mild exposure to roentgen rays or by repeated injections of arsenic, by which methods he prevented tar cancer formation in animals.

This protective phenomenon is still more strikingly demonstrated by Murphy and Sturm in their experimental transplantation of mouse tumor into the brains of rats, guinea pigs and pigeons. Here transplants took well as long as they were entirely in the brain tissue. Once they came in contact with the ventricle or larger blood vessels a cellular reaction took place and destruction of the tumor occurred. Similarly, the transplanted tumor tissue was destroyed when a bit of autologous spleen tissue was transplated simultaneously with the tumor tissue. Here again the defensive action of connective tissue is demonstrated.

In attempting to shed further light on the protecting action of constitutional cancer resistance, Pearce and Brown investigated the subject of experimental metastasis. Although their findings have not given us further definite data about constitutional cancer resistance, they confirm that the peculiarities of metastatic involvement are largely dependent upon constitutional differences of the host which govern the nature and distribution of the lesions and the organs affected.

That cancer production is of infectious origin has again recently been claimed by Robertson, who reports the isolation of organisms of the diphtheroid type from human cancer material, with which, in a few instances, he was able to reproduce cancer in mice. Such findings, while of the utmost interest, demand further proof. Just at present they will have to be classed with those of cancer production by irritation, into which class also falls the gastric cancer produced by Fibiger, cited elsewhere. Neither is the infectious theory of cancer production strengthened by artificial tumor production in plants through inoculation with the bacterium tumifaciens as reported by Blumenthal and Hirschfeld. While it is true that tumor formation in plants can be produced in this way, it is also true that the resulting growth is not of a malignant type since it lacks both the power of penetration and of metastatic transplantation.

In turning to another phase of constitutional cancer resistance, I will briefly review the observations made recently on immunity in relation to cancer. Spontaneous cures of cancer have again been reported by Trinkler. Experimentally, this phase of cancer research has been investigated recently by Woglom, who could not find sufficient proof that either the stroma, or the parenchyma of the tumor, or the vascular changes occurring with the retrogression of the tumor produce the responsible factor in cancer retrogression. More positive findings were reported by Theilhaber, who concludes that since cancer commonly develops in anaemic tissue, it is necessary to raise immunity by stimulation of lymphoid and red blood cell activities. He, therefore, has employed sun and air baths, diathermy and venesection, in conjunction with surgery and radiotherapy, in order to raise immunity by increasing the activities of the circulatory system. His thirty-two "cures" of his forty-four operative cases which he observed during a period of thirteen years, demand that his assumption deserves attention. Of interest is also the report of Russ, who attempts to raise immunity by the injection of radiated cancer tissue previously removed from the host. His report is optimistic, but, like so many others, awaits the test of time.

Nakahara, who investigated the relation of lymphoid activities to cancer immunity, offers proof that such activities are dependent upon certain stimulating or depressing influences, somewhat akin to those governing sensitiveness to foreign proteins. Agents of a depressing character have a similar influence on transplanted cancer. X-ray exerts such a depressing action when a certain dosage is reached.

Applying his conclusions to clinical medicine, we cannot help but wonder if this principle does not explain the dismal failures of repeated deep radiation with massive doses of roentgen rays, where a patient, who apparently had improved marvelously after one exposure, failed rapidly after further treatments.

Numerous workers have attacked the cancer problem by studying the associated biology. The instances are by far too numerous to be reviewed here, especially so since they fail to give us essentially new information which might be of value to the clinician. The vast majority of the biological phenomena, which appear with cancer progress, must be attributed to secondary manifestations, such as anemia and cachexia. I, therefore, pass over this phase of cancer research and go on to studies of the influence of experimental radiation on cancer.

Leo Loeb has recently reviewed the literature on the effects of roentgen rays and radioactive substances on living cells and tissues. He has come to the conclusion that the main effect of radiation on tumors consists in a direct injurious effect on the tumor cells. A secondary effect is expressed in reactions of the host, which hold in check or injure still further, for variable periods, tumor cells primarily injured by radiation. He also points out that results, in which the number of lymphocytes was increased by radiation resulting in a retardation of transplanted tumors cannot, as yet, be applied to man. That there are other factors than those cited by Loeb has been claimed by Schwarz. This author believes that the specific roentgen ray sensitiveness of some carcinomas is proportionate to the tendency toward involution of the organ from which the growth originated, as, for instance, in the case of the uterus. Also Murphy, Maisin and Sturm hold that radiation of the tumor cell is not the only factor which governs cancer retrogression. These investigators found that autografts of spontaneous mouse cancer, when implanted into an area previously exposed to an erythema dose of x-ray, failed to grow in more than 70 per cent of their trials. Similarly, growing autografts would also disappear in about the same proportion if the tumor and the surrounding tissue had been exposed to an equal dose. On the other hand, autografts exposed to the same dosage outside of the body and then implanted grow progressively in 96 per cent. Their conclusion was that roentgen rays had done no direct damage to the cancer cells. To strengthen their deduction they rayed tumor tissue in situ and then transplanted it, finding that it would grow actively in the new host. Their work has been essentially substantiated by Nakahara, who also noted the increased lymphoid activity over polymorphonuclear reaction in radiated areas.

That cancer transplants will still grow after massive radiation has been claimed individually by Kok and Vorlaender. Both these investigators hold that the activity of rays is, therefore, not necessarily of a local character. They are convinced that it is the smaller (stimulating) dose which incites the production of some defensive substance most likely of the nature of a connective tissue-growth stimulant because connective tissue reactions fail to materialize if this tissue has been damaged by overmassive doses.

It is quite clear that most of the recent findings point toward a cancer-controlling substance of constitutional origin, which experimentally can be increased or decreased at will. This, to my mind, is the most momentous advance in cancer research. The unsolved portion of the problem is to locate the seat or seats of origin of this controlling influence.

Researches under way at present suggest that the endocrine system may be a definite factor in this respect. Although we all realize that the endocrine theories have been worked to death, it, nevertheless, remains a fact that these glands, as a whole or in part, constitute the governors of our most important body functions. We, therefore, cannot disregard the findings which Engel has reported on the relation of the endocrines to cancer growth. Engel has succeeded in inhibiting tumor transplants in mice effectively by the injection of thymus, and to a lesser degree by injections of thyroid derivatives. He found ovarian and testicular products ineffective, but noticed that pituitary substances had a growth-stimulating influence. In his conclusions he points out that these activities are not pharmacodynamic, but hormonal in nature, since they do not depend upon albuminous bodies of high molecular structure, but rather upon abiuretic, well broken down, albuminous products similar in nature to Abderhalden's optones. Engel is very cautious, and sounds a warning in regard to the source of the endocrine materials utilized since their qualitative as well as quantitative effects are governed by age, race and species. In defense of his experimental evidence he cites the beneficial influence of oophorectomy in operable cancer of the breast, which he explains by the retroactive stimulation produced in the thymus. Whatever truth there is in Engel's findings, a vast and hopeful field has been opened for further research. To me it is a sign that we are approaching a solution of the phenomenon which determines the constitutional resistance against cancer. Were it not for the enthusiasm and optimism among the workers in cancer research, we might just as well resign ourselves to be ultimately doomed to destruction by cancer, although such a fate lies so far ahead in the dimmest future that we cannot measure it by our standards of time.

There are numerous other questions on cancer research left undiscussed here because of their highly technical and hypothetical nature. In the main I have touched on the most vital findings which have a direct bearing on the clinical aspect of cancer. In summing up I repeat that recent cancer research has definitely shown that malignancy can no longer be regarded as a local manifestation alone, but must be accepted as a constitutional disturbance. Cancer research has opened up new aspects of cancer treatment which may take on concrete forms as research progresses and which ultimately may materialize into more successful methods of treatment.

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DISCUSSION

EDWARD NORTON EWER, M. D. (Federal Realty Bldg., Oakland)—Until recently we were advised that the only definite thing known about cancer etiology was the

requirement of a pre-existing irritant lesion. While this does not yet recede in importance, it is interesting to know of the new place in the sun being accorded to heredity and that nebulous factor, constitutional resistance, which seem likely to bring cancer into the class of systemic diseases. Doctor Emge's paper is a clear and timely resume of recent cancer research.

Belief in heredity seems to be gaining ground, but whatever role it plays in the matter is of no practical importance so far as man is concerned, for selective breeding is, of course, out of the question. Human mating is not arranged on a health betterment basis. Eugenics, at present, is only an academic pastime for certain intellectuals.

It is interesting to note the change in view in regard to constitutional tendency; and the passing of the teaching that cancer is, in its beginning, a local disease always amenable to cure by extirpation, if discovered early enough. True, we are still to gauge our treatment according to that view; and the educational propaganda to bring the patient to early treatment must go on. It is shown that local irritations long continued cause cells to lose their normal character and revert to embryonal type when they take on the rapid growth characteristic of embryonal tissue. This displaces Conheim's theory of embryonal rests. Another factor in proof of the constitutional influence and against the Conheim theory, is the occurrence of multiple primary cancers. They are not very common, but many cases have been reported by various authors. Kocher contributed a case of simultaneous primary occurrence in ovary, breast and axilla. Multiple cancers of various types occur at the same time and malignancy of different types as well, not only in paired organs but in those differing in function. Davidsohn reports a case of chorionepithelioma and primary gastric carcinoma existing together. Carcinoma in one place and sarcoma in another have been described.

While then cancer as a systemic disease is almost established, we must, as already stated, continue our attempts at the earliest eradication possible. The so-called "precancerous" stage must be looked for. The denial of a recognizable precancerous condition (Pick and Hansemann) is one of the "great hindrances in the recognition of early carcinoma" (L'Esperance.) It may not be possible to state that a particular lesion will later become cancer, because we have no means as yet to determine the individual degree of constitutional cancer resistance, but we have some facts to guide us in handling these lesions. We know the danger for the future in gastric ulcer. Epidermal and subepidermal tumors of certain types should be excised (Bloodgood). Erosions of the cervix and cervical polyps in the cancer age are portents of evil; and many experienced surgeons are beginning to urge the removal of a uterus, from the cervix of which there is an intractable discharge as the menopause approaches.

The great expenditure of time and money in cancer study is gradually making returns, and we are warranted in looking with confidence for more effective treatment in the early future.

ALSON R. KILGORE, M. D. (391 Sutter Street, San Francisco)—Doctor Emge's excellent survey of recent cancer research leaves one with the conviction that we are still wandering in a maze of more or less disconnected facts. The factor of heredity in the incidence of cancer is coming to be more and more accepted, but the relation of cancer origin and growth to the fibro-blast and lymphocyte mechanisms, to endocrine dysfunction and even to such external influences as radiation, are still largely in the realm of speculation. Many suggestions have come from research along various lines, but we are still unable to correlate the separate bits of knowledge obtained into any connected explanation of the cancer process.

There are, as brought out in this paper, several pieces of evidence pointing to general systemic changes taking place in association with cancer, perhaps resulting from the cancer—possibly causing or predisposing to the development of cancer. There is even some evidence that experimental cancer may produce immunity against further development of similar cancers.

But, after all, whatever the final verdict of research, for practical purposes in the clinical handling of the disease, the vast majority of human cancers behave as if their origin were purely local. Certainly, the only treatment so far productive of permanent cures has been mechanical destruction or removal of cancer cells before unreachable metastasis has taken place. For the present, therefore, we ought to distinctly recognize two phases of the cancer problem—the research problem for what the future may bring—the public's problem of the present reduction of cancer mortality. In the attack on the community's present cancer problem, we have still to go on the assumption that cancer begins as a local disease and educate our public to recognize the danger-signals of cancer in its early stages.

HERBERT W. WALL, M. D. (6331 Hollywood Blvd., Los Angeles)—Doctor Emge is to be highly commended upon his able manner of handling this most important subject. All of the resources of chemistry, physics, physiology, biology, and the study of immunity reactions, have, during the past few years, been brought to bear upon this problem. Although some things have been achieved, we have yet a long way to go. Experimental work on animals has been productive of many things; ofttimes as much on the negative as on the positive side.

The knowledge that manipulation and compression often produce metastases, must be kept more prominently before us. Even subsequent to operative interference, it must be recognized that such factors are of great importance. Early operative removal of all conditions simulating carcinoma, should be the physician's attitude, without debating unduly and losing valuable time, which so often seals the fate of many a case that comes to us, long after a reasonable diagnosis has been made, and the patient tarried while the family physician failed to urge immediate action. It is the early and uncertain cases that must be recognized, if any material improvement in our mortality is to be brought about. The physician who fails to make a thorough physical examination and then follow up by every known test to arrive at a diagnosis, is guilty of criminal negligence, and his patient will later reap the inevitable consequence. One need not be an alarmist, but simply be on the alert at all times to perceive the significance of his patients' symptoms.

Removal of tissue for pathological examination is impossible in many conditions before the time of operation, and in these cases it should be avoided, if a diagnosis can be made with reasonable certainty by other methods. But where it is necessary in a doubtful case one must be prepared to follow up immediately by the radical measures which the case may demand. In dealing with incipient carcinoma, the two courses open to the physician are: (1) to await further developments, (2) to make an exploratory, to be followed at once by a radical operation if the diagnosis is positive. The first method is often the easier course, and, sad to relate, is still followed by a great many men, and it is one of the factors most directly responsible for the present enormous mortality of this disease. Let us resolutely abandon this attitude, and, by our eternal vigilance and prompt action, cut down the death rate in carcinoma, just as has been done during the past two decades in the case of appendicitis.

DOCTOR EMGE (closing)—I greatly appreciate and agree with the thorough and frank discussions presented here. If my presentation of the subject has given the impression that I advocate any deviation from the accepted radical treatment of isolated malignancies, I wish to go on record right now that I believe in the most radical methods of attack employed at the earliest moment. The subject of this review deals primarily with basic factors in the biology of cancer and not with its treatment. The reason for presenting it was to acquaint the general profession at large with certain advances which ordinarily do not come to the attention of the general practitioner because of the limited time he can devote to reading of specialized journals.